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10/814,826	03/31/2004	Pamela J. Fereira	3139-6351.1US (ALZ5019/32	5280

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EXAMINER	
FRAZIER, BARBARA S	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,826	FEREIRA ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-31* is/are pending in the application.

4a) Of the above claim(s) *9,14 and 18-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-15 and 17-31 are pending in this application. Claim 16 stands canceled.

2. Claims 18-31 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/28/07.

3. Claims 9 and 14 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/28/07.

4. Claims 1-8, 10-13, 15, and 17 are examined.

Double Patenting

5. The provisional rejection of claims 1-8, 10-13, 15, and 17 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-37 of copending Application No. 11/183,477 is withdrawn in view of Applicant's Terminal Disclaimer filed 3/2/10.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-8, 10-13, 15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berry et al (WO 00/45790) and Chen et al (US 2003/018036), in combination alone or further in view of Kasraian et al (Pharm. Dev. And Tech., 4(4) 475-480, 1999) and Hunt (US 2003/0064536).

The claimed elected invention is drawn to a stable nonaqueous drug formulation comprising at least one drug; and a nonaqueous, single-phase vehicle comprising at least one polymer and at least one solvent, the vehicle being miscible in water, wherein the drug is insoluble in one or more vehicle components and the drug formulation is stable at 37 degrees C for at least two months, and wherein the polymer was treated with methionine in an amount sufficient to reduce vehicle peroxide values below 5 ppm (see claim 1). Applicants have elected the species wherein omega-interferon is the drug, polyvinylpyrrolidone is the polymer, and benzyl alcohol is the solvent.

a) The rejection over Berry et al and Chen et al alone

Berry et al disclose stable non-aqueous single phase viscous vehicles and formulations comprising at least one beneficial agent uniformly suspended in the vehicle (abstract). The vehicle comprises polymer and solvent (page 6, lines 17-18) wherein the polymer is about 5% to about 30% and the solvent is about 30% to about 50% of the

vehicle (page 6, lines 20-22). The beneficial agent may be peptides or proteins that have biological activity or that may be used to treat a disease or other pathological condition, such as interferons (page 13, lines 29). The "polymer" includes polyesters such as PLA, pyrrolidones such as polyvinylpyrrolidone, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers; preferred polymer is polyvinylpyrrolidone (page 12, lines 15-22). The formulations may be stored at temperatures ranging from cold to body temperature (about 37 degrees C) for long periods of time (1 month to 1 year or more) (page 6, lines 27-30).

While Berry et al suggest the use of solvent with the polymer, as well as beneficial agents such as interferons, Berry et al do not specifically teach the use of benzyl alcohol as a solvent or omega-interferon as the interferon used as the beneficial agent. The formulation is also not taught as being miscible in water.

Chen et al teach catheter injectable depot compositions comprising polyvinylpyrrolidone polymer (paragraph 75) and benzyl alcohol solvent (paragraph 76); experimental data using the formulations made reveals that compositions comprising benzyl alcohol as the solvent show an improvement by reducing the injection force of the depot gel formulation (Examples 15 and 17). Chen et al also teach that omega-interferon may be used as the beneficial agent (paragraph 178), and that the compositions comprising polyvinylpyrrolidone and benzyl alcohol have a measure of miscibility in water (paragraph 21). Both the formulations of Berry et al. and the compositions of Chen et al. are drawn to compositions comprising interferon, polyvinylpyrrolidone, and solvent, to be used in drug delivery systems.

It is generally considered to be prima facie obvious to combine components each of which is taught by the prior art to be useful for the same purpose in order to form a composition that is to be used for an identical purpose. The motivation for combining them flows from their having been used individually in the prior art, and from the being recognized in the prior art as useful for the same purpose. As shown by the recited teachings, instant claims are no more than the combination of conventional components of compositions for drug delivery systems. It therefore follows that the instant claims define prima facie obvious subject matter. Cf. In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

Therefore, it would have been prima facie obvious at the time the invention was made to form a stable, nonaqueous composition by combining the interferon, polyvinylpyrrolidone and solvent of Berry et al. with the omega-interferon, polyvinylpyrrolidone and benzyl alcohol of Chen et al. in order to arrive at the claimed invention, with a reasonable expectation of success.

With respect to the drug being insoluble in one or more vehicle components (claim 1), Berry et al. teach that the beneficial agent is uniformly suspended in the vehicle (not solubilized), and thus would not be soluble in at least one of the vehicle components.

With respect to the polymer being treated with methionine in an amount sufficient to reduce vehicle peroxide values below 5 ppm, it is noted that the limitation “the polymer was treated with methionine" is a product-by-process limitation. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113. In the instant claims, the limitation of treating the polymer with methionine to reduce peroxide values does not appear to impart a structural limitation to the formulation, other than the amount of peroxide values. To that end, Berry et al teach that peroxides “not only adversely affect protein

stability but would be toxic when delivered directly to, for example, the central nervous system of a human or animal" (page 4, lines 23-24), although Berry is silent as to the peroxide values of its own compositions. Still, since Berry et al teach that the formulations may be stored at temperatures ranging from cold to body temperature (about 37 degrees C) for long periods of time (1 month to 1 year or more) (page 6, lines 27-30), one skilled in the art would assume that the peroxide values of the formulations made by Berry et al and Chen et al would also be less than 5 ppm, especially given the fact the components and use of the compositions of Berry et al. and Chen et al and the compositions of the claimed invention are the same. Therefore, the process limitation of treating the polymer with methionine does not impart any additional structural limitation to the formulation other than what is already taught in the prior art.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Since Applicants have not provided any objective evidence that the formulation of Berry et al and Chen et al do not have peroxide values of less than 5 ppm, the rejection is maintained.

b) The rejection over Berry et al and Chen et al, and further in view of Kasraian et al and Hunt

However, should the formulation of Berry et al and Chen et al not possess the characteristic relied on (i.e., not have peroxide values of less than 5 ppm), and/or should the process step of treating the polymer with methionine impart a structural

limitation other than what is taught in the references of Berry et al and Chen et al, the Examiner relies on the teachings of Kasraian et al and Hunt to demonstrate that said process step would be obvious to one of ordinary skill in the art.

The inventions of Berry et al and Chen et al are delineated above.

Kasraian et al teach that polymers, such as PVP, often carry low levels of peroxides, which affect the stability of the product, as evidenced by color change. Control of the peroxides as trace impurities is suggested (see pages 476 and 477). The teachings of Kasraian et al are drawn to injectable formulations (see title).

Hunt teaches that peroxides can be reduced by inclusion of an amino acid which can act as an oxidative sink, that is, as a scavenger for oxidizing compounds. A particularly preferred amino acid is methionine (see paragraph 117). The invention of Hunt is also drawn to injectable formulations (for example, see paragraph 141).

It would have been obvious to a person having ordinary skill in the art of injectable formulations to treat a polymer such as polyvinylpyrrolidone with methionine in order to reduce peroxide values below 5 ppm; thus arriving at the claimed invention. Kasraian et al fairly teaches that excipients such as PVP carry levels of peroxides, and Hunt fairly teaches that methionine reduces said levels of peroxides. Therefore, one skilled in the art would be motivated to treat the PVP to be used in a formulation (such as that of Berry and Chen) with methionine in order to reduce peroxide value levels below 5 ppm. One would reasonably expect success from said process because the teachings of Kasraian et al and Hunt are both drawn to formulations suitable for

delivering a drug, as are the inventions of Berry et al (page 7) and Chen et al (see abstract).

With respect to the amount and method of degradation of the drug (claims 2 and 3), Berry et al do not specifically teach the percentage of drug degraded by chemical pathways or aggregation. However, Berry et al. do teach that the formulations maintain a high level of stability over time, wherein greater than 70% of the formulation is recovered at seven weeks (Tables 5 and 6). Based on this data, one skilled in the art would conclude that the level of degradation of the formulations would be comparable to that described in the claimed invention.

With respect to the drug being a particulate material (claim 4) that is dry (claim 12) and dispersed with the vehicle as a suspension (claim 17), Berry et al. teach that the active agent is buffered, then spray dried (page 16) before forming a uniform dispersion (page 17); Berry et al. also teach that drying the beneficial agent prior to formulation enhances the stability of the formulation (page 15).

With respect to the choice of drug (claims 5-7), Berry et al teach that the beneficial agent may be interferons (page 13, lines 29), and Chen et al teach that omega-interferon may be used as the beneficial agent (paragraph 178).

With respect to the choice of polymer (claims 8 and 15), Berry et al teach that the preferred polymer is polyvinylpyrrolidone (page 12, lines 15-22), and Chen et al teach compositions comprising polyvinylpyrrolidone polymer (paragraph 75).

With respect to the viscosity of the formulation (claim 10), Berry et al. describes the vehicle of the formulation as a "viscous vehicle", which means a viscosity that is preferably about 10,000 to 250,000 poise; this is encompassed by Applicant's viscosity of about 1,000 to about 250,000 poise.

With respect to the amounts of polymer and solvent (claim 11), Berry et al. disclose that the amount of the polymer is about 5% to about 30% and the amount of solvent is about 30% to about 50% of the vehicle (page 6, lines 20-22). This appears to be comparable to the amounts claimed by Applicants, especially given that the prior art uses the flexible modifier "about". In any case, it would have been obvious to determine workable and/or optimal amounts of polymer and solvent per the reasoning of well-established precedent, such as In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). (Holding that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.")

With respect to moisture content (claim 13), Berry et al. teach that the final moisture content of the viscous vehicle was less than 2% (page 15, line 2).

With respect to the choice of solvent (claim 15), Chen et al teach that the compositions comprise benzyl alcohol solvent (paragraph 76), and that experimental data using the formulations made reveals that compositions comprising benzyl alcohol as the solvent show an improvement by reducing the injection force of the depot gel formulation (Examples 15 and 17). Therefore, one skilled in the art would be motivated

to select benzyl alcohol as the solvent due to the improved properties of said solvent, with a reasonable expectation of success.

Response to Arguments

8. Applicant's arguments filed 3/2/10 have been fully considered but they are not persuasive.

Applicants first argue that Berry teaches that its polymers do not contain peroxides and are therefore better than using the lipid system [of the prior art] that would contain peroxides. Applicants argue that Berry believed that use of their polymer formulation would avoid peroxide problems as seen with prior lipid vehicle formulations. Applicants argue that Chen does not teach applicants' recited formulation, failing to mention peroxides.

This argument is not persuasive. While Berry teaches that other compositions of the prior art can result in the formation of peroxides (page 4), Berry is actually silent as to whether or not peroxide formation results from its formulation; Chen also is silent on the matter, since it does not mention peroxides. As stated in the rejection, though, one skilled in the art would assume that the peroxide values of the formulations made by Berry et al and Chen et al would also be less than 5 ppm, especially given the fact the components and use of the compositions of Berry et al. and Chen et al and the compositions of the claimed invention are the same. However, should the formulation of Berry et al and Chen et al not possess the characteristic relied on (i.e., not have peroxide values of less than 5 ppm), and/or should the process step of treating the

polymer with methionine impart a structural limitation other than what is taught in the references of Berry et al and Chen et al, the Examiner relies on the teachings of Kasraian et al and Hunt to demonstrate that said process step would be obvious to one of ordinary skill in the art. Applicant's assertions that the combination of Berry and Chen teaches that use of polymer systems would avoid the peroxide problems seen with liposomes, and that a number of polymer systems can be usefully developed and used without having any reported problems with peroxide contamination, appears to support the Examiner's position that the combination of Berry and Chen reads on the claimed invention. As pointed out in the previous Office action, the limitation "the polymer was treated with methionine" is a product-by-process limitation. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113. If Berry et al teach that use of their peroxide formulation would avoid peroxide problems, and if the failure to mention peroxides in Chen implies that a peroxide problem is not present, as Applicants assert, then the limitation of previously treating the polymer with methionine in an amount sufficient to reduce vehicle peroxide values below 5 ppm does not impart any additional structural limitation to the formulation other than what is already taught in the prior art, absent evidence to the contrary. Applicants have not provided any objective evidence that the formulation of Berry et al and Chen et al do not have peroxide values of less than 5 ppm.

In response to applicant's arguments against the references individually, namely, that Kasraian and Hunt do not teach applicant's recited formulations (page 10 of

Remarks), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the rejection, the teachings of Kasraian and Hunt are relied upon to show that, should the product-by-process limitation of treating the polymer with methionine to reduce vehicle peroxide values below 5 ppm impart a structural limitation to the formulation, said process step would be obvious to one skilled in the art for reasons stated above. One skilled in the art would look to the teachings of Kasraian and Hunt and consider them relevant to the teachings of Berry and Chen, since the teachings of Kasraian et al and Hunt are both drawn to formulations suitable for delivering a drug, as are the inventions of Berry and Chen.

In response to applicant's arguments against the references individually, namely that Berry teaches away from the claimed invention, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection is based not on Berry alone, but rather Berry in view of Chen (alone or further in view of Kasraian and Hunt); as stated in the rejection, the deficiencies of Berry are cured by the teachings of Chen regarding choice of solvent and interferon.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon

hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

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